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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,615	07/08/2003	Clemens Hendricus, M. Kocken	2183-6041US	8276

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/615,615	KOCKEN ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6 and 8-45* is/are pending in the application.

4a) Of the above claim(s) *11-26 and 31-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8-10,27-30 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 11/16/2005, canceling claims 5 and 7, amending claims 1, 3, 8, 11, 13, 14, 24, 27, 28, 31, 43, 38, 40, 41, and 44, as well as adding new claim 45. Pursuant an election without traverse in response to a restriction requirement, claims 11-26 and 31-44 are withdrawn from consideration as drawn to non-elected subject matter (See Non-Final Action, mailed 9/17/2004). It should be noted that a complete reply to a final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-4, 6, 8-10, 27-30 and 45 are under consideration in this action.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. As no new grounds of rejection are set forth that are not necessitated by material changes to the claims **this action is made FINAL**.

Response to Amendment

The amendment of independent claims 1 and 27 (as well as new claim 45) does not substantially change the scope of the claims. Applicant's arguments in traversal of the rejections repeated herein are based primarily on said amendments thus it is instructive to clarify the effect of such amendments. In salient part the amendments recite the following in methods of producing mRNA or a protein (claims 1 and 27 respectively):

> "providing a yeast cell with a nucleic acid encoding said ectodomain or *functional part thereof*, wherein said nucleic acid *has a sequence* as depicted in FIG. 1 [SEQ ID NO: 6], *or* wherein said nucleic acid *has a sequence that comprises* at least 90 percent homology *to a sequence* as depicted in FIG. 1..." (Emphasis added)

In addition, the preamble of each independent claim is also directed to expression of any "functional part" of *Plasmodium falciparum* apical membrane antigen-1 (AMA-1). The limitation "functional part" is extremely broad and ambiguous, and as such the claims encompass an essential element/critical feature, which encompasses a large number of species within a genus of nucleic acid fragments that correlate to the functionality of "comprising at least one expression characteristic". (See Specification, ¶ 0017, broadly defining "functional part"; note: all references to the specification correspond to the published version of this application, i.e., 2004/0091971). Put another way, the claims literally read on at least any two amino acid residues that occur in any at least 30 base pair region of SEQ ID NO: 6 and that correlate to some undefined expression characteristic. (Id., last sentence reciting, "By at least functional part of a nucleic acid...[it] is meant a part of said nucleic acid [FIG. 1], at least 30 base pairs long...comprising at least one expression characteristic..."). As such, and notwithstanding the instant amendment to the base claims, the invention encompasses a vast genus of nucleic acids encoding fragments having at least a sequence that corresponds to any stretch of two amino acid residues (6 nucleotides) within any 30 nucleotides, as depicted in Fig. 1. As a result, and where the sequence depicted in Fig. 1 is over 1.8 kb, the claimed genus encompasses potentially thousands of embodiments meeting the structural limitations and corresponding to the extremely broad and undefined functionality of "at least one expression characteristic". (Specification, p. 4, continuation of ¶ 0017).

As to the limitations of *Plasmodium falciparum* AMA-1, it must be noted that as written, the claims are not actually directed to a step of providing a nucleic acid encoding *Plasmodium falciparum* AMA-1 as is presumably intended. Rather, the claims are defined by a structural

limitation where in a process of producing any *functional part* (i.e., mRNA and peptide/polypeptide, claims 1 or 45 and 27 respectively), the nucleic acid encoding said fragment (mRNA or peptide) is at least 90 percent homologous to *any* sequence depicted in Fig. 1. Such an interpretation is proper, because the claims recite the indefinite article "a" in defining the structural requirements for any *functional part* in relation to *a sequence* as depicted in FIG. 1 [SEQ ID NO: 6], *or* wherein said nucleic acid *has a sequence that comprises* at least 90 percent homology *to a sequence* as depicted in FIG. 1. For example, if the claims were to recite "90 percent homology to *the* sequence" then the quantity and substance for the written description requirement would be significantly reduced. The definite article "the" would clearly and unambiguously direct the claim to the entire sequence depicted in Fig. 1 instead of any subsequence disclosed therein.

In addition, as a result of the ambiguity ascribed to the limitation *functional part* as discussed above, the limitation "exhibits specificity for mAb 4G2" is correspondingly very broad and ambiguous. For example, when interpreted as broadly as reasonable, said limitation can be interpreted to mean that the reference sequence (Fig.1 or SEQ ID NO: 6, which encodes a *P. falciparum* AMA-1) exhibits specificity for mAb 4G2 and is merely the reference sequence from within which sequences encoding a *functional part* are selected. In other words, under such an interpretation, **the limitation for mAb 4g2 specificity does not substantially or materially delimit the functional part(s) that are expressed but only provides a characteristic for the reference AMA-1 sequence as depicted in Fig. 1.** Thus, as long as a reference teaches expression of a *functional part* that meets the structural limitation of comprising at least 90 percent homology to *any sequence* within that of Fig. 1, and lacking a glycosylation site, then

said reference would meet the claimed limitation of expression a *functional part* of a *P. falciparum* AMA-1 where said *P. falciparum* AMA-1 exhibits specificity for mAb 4G2. In effect as written, the claim recites limitations that do not correlate to the nucleic acids provided to the yeast cell that encode *functional parts* but instead delimit the reference sequence from which any one of thousands of sequences are defined by structural limitations discussed in the foregoing.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 1-4, 6, 8-10, 27-30 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection is of record and incorporated by reference herein as applicable to the limitation "functional part". The rejection is new insofar as it is applied to new claim 45. A response to Applicant's argument is set forth below immediately following a recitation of some salient portions of the rejection of record. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More specifically the claims are directed to a genus of nucleic acid molecules that encode *any* functional part of a *P. falciparum* AMA-1 ectodomain, where the *functional part* is defined by any sequence comprising at least 90 percent homology to any sequence as depicted in

Fig. 1, and where said *functional part* lacks at least one glycosylation site. Thus, said *functional part(s)* constitute a critical component for practicing the claimed methods and said component correlates to the function that is extremely broad. (See, Response to Amendments, for an explicit interpretation of the claims, *supra*).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that as amended the claims comply with the written description requirement. In particular, Applicant asserts that the limitations "functional derivative", "functional analogue" and "combination" are deleted, and the claims are now defined by specific structural requirements (i.e., 90 percent homology to Fig. 1 and lacking a glycosylation site).

The amendments do not sufficiently narrow the number of potential embodiments within the genus comprised of "functional parts". (See, Response to Amendments, *supra*). The specification teaches that in *Plasmodium falciparum* the AMA-1 spans amino acid residues 25 to 545 (e.g., p. 4, last ¶). However, the claims are directed to nucleic acids encoding any *functional* portion as defined by the structural requirements of having at least 90 percent homology *to a sequence* as depicted in Fig. 1. Thus in contrast to what is presumably intended – limiting the claims to nucleic acid molecules encoding AMA-1 protein from *P. falciparum* – the claims still encompass thousands of possible *functional parts* (i.e., fragments) within *any 30 bp region* of said approximately 1.8 kb sequence depicted in Fig. 1. In other words, the claimed methods are defined by utilization of a structural component that *is not* necessarily obtained from *P. falciparum*.

Rather, any sequence meeting the structural requirement of having any sequence comprising at least 90 percent homology to *any* sequence (within an at least 30 bp region) of SEQ ID NO: 6. By Applicants own assertion, a mere five examples (i.e., functional parts) have been provided (Specification, p. 10, ll. 16-25). Of the five only three are show to reactive with the parasite-inhibitory antibody. (e.g. p. 24, bottom ¶). Such a limited disclosure cannot be deemed sufficient to possess the genus of thousands of *functional parts* derived from *P. falciparum*, as defined by the structural requirements discussed herein above. Based on the description provided and the knowledge in the art, one of skill is unable to envisage a representative number of *functional parts* that are produced by the claimed process and that correlate to the disclosed function of "comprising at least one expression characteristic". Further, if it were asserted that the corresponding functionality is the specificity of mAb 4G2 to the *functional part* expressed, then it must be noted that as written the claim is not directed to such an embodiment. (Supra, Response to Amendments). In view of the foregoing, the instant disclosure fails to meet the written description requirement. Therefore, there is insufficient justification to permit an applicant to engross a broad field where neither the disclosure or the art identify a representative number of products produced by the claimed process that have the prescribed utility. This rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claims 1-3, 5-6, 9-10, 27-30 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Kocken et al. (Infect. Immun. 1999 Janurary; 67(1):43-49; see whole document).**

This rejection is of record and incorporated by reference herein as applied to the instant claims. The claims are interpreted consonant with what is stated above. (Supra, Response to Amendments). The rejection is repeated in salient part. A response to Applicant's argument is set forth immediately following the body of this rejection. The claims are directed to expression of any *functional part* of *P. falciparum* AMA-1 wherein at least one glycosylation site is removed and said *functional part*. The limitation, "modified" is interpreted as broadly as reasonable to read on any change/alteration of the site (e.g. enzymatic or structural).

Kocken et al. teach expression of *P. vivax* AMA-1 in *P. pastoris* to elicit protective immunity in *Macaca mulatta* monkeys. (e.g. Abstract). More particularly, particular sites that are normally glycosylated are mutagenized so as to preclude subsequent glycosylation. (e.g. p. 44, col. 1, ¶ 3). In addition, the proteins expressed are purified through such steps as dialysis, precipitation or ion exchange chromatography. (e.g. p. 44, last ¶, bridging to col. 2). In sum, Kocken et al. anticipates the rejected claims.

The limitation of claims 1 and 27 recites in salient part, "[S]aid nucleic acid being *modified* to utilize said yeast cell's codon usage." (emphasis added). If one of skill were to read the relevant corresponding passages in the specification, a reasonable interpretation is that *modification* is removal of at least one glycosylation site so as to enhance expression in a particular host cell, such as yeast.

Notably, the specification teaches that the nucleic acids encoding AMA-1 is modified so as to utilize a yeast's codon usage. (e.g., p. 10, ll. 11-12). Most notably, the specification teaches that said modification includes removal of at least one site that is generally glycosylated by a eukaryotic expression system. (e.g., p. 9, ll. 21-30; p. 3, ll. 1-11). The limitation "codon usage" is interpreted as broadly as reasonable in light of the instant disclosure's teachings to mean modification of a nucleic acid to utilize a yeast cell's codon usage to enhance expression. Therefore, as stated above, Kocken et al. teaches a nucleic acid that is modified to utilize the *P. pastoris* codon usage. (e.g., p. 44, col. 1, ¶ 3).

With respect to the structural limitation for a expressing a "functional part" that comprises a sequence having at least 90% homology to a region in the sequence of SEQ ID NO: 6, and that lack a gylcosylation site. It should be noted that the claims as written do not actually read on an action step of removing/modifying a residue so as to remove a glycosylation site, but instead, the claims are defined by providing a yeast cell with a nucleic acid encoding a peptide/polypeptide that meets a certain structural limitation of lacking at least one glycosylation site. Kochen *et al.* teach expression of a nucleic acid encoding a *functional part* (i.e., AMA-1 of *P. vivax*), which inherently comprises multiple sequences that have at least two or more amino acid residues in common with the sequences depicted in SEQ ID NO: 6 and that lack a gylcosylation site. For example, in the amino portion of the *P. vivax* AMA-1, the amino acid residues D-I-E correspond to the same residues in a sequence depicted in Fig. 1, and lack a glycosylation site. (See Michon et al. Mol. Biol. Evo. 2002; 19(7):1128-42, p. 1134, Fig. 4,

depicting partial sequences for *P. vivax* AMA-1, first set of alignments, line 3, as compared to instant Fig. 1, line 8)[1]. In sum, Kochen *et al.* anticipates the rejected claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that in view of the amendments delimiting the claims to *P. falciparum* the teachings of Kochen *et al.* directed to expression of *P. vivax* are patentably distinguishable. (Remarks, p. 10). Applicant does not assert any additional arguments.

As is explained in the interpretation of the claims in the rejections above and Response to Amendments, the limitations of *P. falciparum* do not actually delimit the *functional part* fragments to which the claims are directed. (See, Response to Amendments, *supra*). Rather, the limitations for *P. falciparum* and mAb 4G2 specificity merely characterize the reference sequence from within which nucleic acid sequences are selected to express *functional part(s)* meeting the structural limitation of comprising at least 90 percent homology to *any* sequence from within the over 1.8kb sequence of Fig. 1/SEQ ID NO: 6 and that lack at least one glycosylation site. Thus, for the reasons provided herein above, this rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

[1] Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to show that a characteristic not disclosed in the reference is inherent. *See* MPEP § 2131.01.

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. **Claims 1-4, 6, 8-10, 27-30 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kocken et al., and further in view of Withers-Martinez et al. (Protein Engineering. 1999; 12(12): 1113-1120; see entire document).**

This rejection is of record and incorporated herein in its entirety as applied to the instant claims. A response to Applicant's arguments is set forth immediately below. This application currently names joint inventors.

Response to Arguments

Applicant's does not set forth any arguments in response to this rejection. Presumably, Applicant relies on arguments set forth relative to Kochen et al. Thus, for the reasons set forth above, this rejection is maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

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